MUTATION IN BRIEF

Familial Melanoma, Pancreatic Cancer and Germline CDKN2A Mutations

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Germline CDKN2A mutations have been observed in approximately 20 percent of familial melanoma kindreds from North America, Europe and Australasia. There is also an increased risk of pancreatic cancer in a subset of families with mutations, however, the precise relationship between the CDKN2A gene and pancreatic cancer remains unknown. The relationships between familial melanoma, pancreatic cancer and germline CDKN2A mutations were examined using published data. There were 67 different CDKN2A mutations in 189 melanoma-prone families. Forty-two families (18 mutations) had pancreatic cancer reported. For families without reported pancreatic cancer, the most common types of mutations were missense (56%), frameshift (12%), and deletions (12%). For families with pancreatic cancer, missense (56%), splicing (17%), and frameshift (11%) mutations were most common. Seventy percent of the mutations were observed only once, while the remainder recurred in different families. Comparison of 147 melanoma-prone families without pancreatic cancer to the 42 families that had pancreatic cancer reported showed no significant differences in the types or locations of mutations. However, there was a significant difference (p=0.002) in the distribution of families across the four ankyrin repeats. This finding primarily resulted from the six most frequent mutations where the distribution of pancreatic cancer varied significantly (p=0.02) from at least 30% in c.301G>T (p.G101W), c.225_243del19 (p.P75fs), c.337_338insGTC (p.R112_L113insR), and c.377T>A (p.V126D) families to less than 10% in c.71G>C (p.R24P) and c.159G>C (p.M53I) families. Further research utilizing individual-specific data will be required to determine whether these patterns represent etiologic differences or incomplete reporting of cancer and mutation data. Published 2004 Wiley-Liss, Inc.†

KEY WORDS: melanoma; familial; pancreatic cancer; CDKN2A

INTRODUCTION

Cutaneous malignant melanoma (CMM) is a potentially fatal form of skin cancer whose etiology is heterogeneous and complex. Approximately 5-12 percent of malignant melanomas develop in individuals with a familial predisposition (MIM# 155601) (Greene and Fraumeni, 1979; Newton et al., 1993; Cutler et al., 1996; Aitken et al., 1996). Some of the familial clusters occur by chance. Others may occur because family members share the same risk factors such as hair color, eye color, freckling, and skin type. Only a subset of familial melanoma patients likely has an inherited mutation in a melanoma susceptibility gene.

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The CDKN2A (MIM# 600160) gene, located on chromosome 9p21 (Kamb et al., 1994; Nobori et al., 1994), is the major high-risk melanoma susceptibility gene identified to date. CDKN2A encodes two distinct proteins translated, in alternate reading frames (ARFs), from alternatively spliced transcripts. The alpha transcript, comprising exons 1α, 2, and 3 with 156 amino acids, encodes a low molecular weight protein, p16 that contains predominantly four ankyrin (Ank) repeats (Ank1: codons 11-40; Ank2: codons 44-72; Ank3: codons 77-106; Ank4: codons 110-139). The p16 protein inhibits the activity of the cyclin D1-cyclin-dependent kinase 4 (CDK4) or 6 (CDK6) complex (Serrano et al., 1993). These complexes phosphorylate the retinoblastoma protein, allowing the cell to progress through the G1 cell cycle checkpoint (Serrano et al., 1993; 1995). Thus, p16 acts as a tumor suppressor and negatively regulates cell growth by arresting cells at G1. The smaller beta transcript, comprising exons 1β, 2, and 3, specifies the alternative product $p14^{ARF}$. $p14^{ARF}$ acts via the p53 pathway to induce cell cycle arrest or apoptosis (Zhang et al., 1998; Pomerantz et al., 1998).

Germline mutations in CDKN2A have been observed in melanoma-prone families from North America, Europe and Australasia. Overall, CDKN2A mutations have been observed in approximately 20 percent of melanoma-prone families from around the world (Goldstein and Tucker, 2004). Some CDKN2A melanoma-prone families also have pancreatic cancer. Several studies have demonstrated an increased risk of pancreatic cancer among CDKN2A melanoma-prone families (Bergman et al., 1990; 1996; Goldstein et al., 1995; Ghiorzo et al., 1999; Borg et al., 2000; Vasen et al., 2000). In addition, germline CDKN2A mutations have been occasionally found in pancreatic cancer patients and families without familial melanoma (Moskaluk et al., 1998; Gerdes et al., 2000; Moore et al., 2000; Lal et al., 2000a; Barsch et al., 2002; Lynch et al., 2002). However, the precise relationship between the CDKN2A gene and pancreatic cancer remains unknown. The purpose of this study was to examine the relationships between familial melanoma, pancreatic cancer and germline CDKN2A mutations using published data to determine whether any identifiable patterns exist.

MATERIALS AND METHODS

Manuscripts published through 2002 with reported germline CDKN2A mutations in familial melanoma patients were reviewed. For purposes of this study, familial melanoma was defined as the occurrence of at least two first-, second-, or third degree relatives with melanoma. Nucleotides are numbered from the first A of the initiation codon of p16INK4A in the standard nomenclature for mutations employed (Antonarakis, 1998). The numbering and naming of variants follows the approaches used in two online locus-specific variant databases for CDKN2A (GenBank: NM_000077.2) and melanoma (eMelanoBase; www.wmi.usyd.edu.au:8080/melanoma.html ;University of Vermont Biodesktop – CDKN2a Database Project) (Fung et al., 2002; Greenblatt et al., 2003). The reporting of pancreatic cancer in these families was also collated. A family was classified as having pancreatic cancer regardless of whether the pancreatic cancer patient was tested for the family's CDKN2A mutation. For many publications, individual-specific data on CDKN2A mutation status and/or pancreatic cancer was not available. Thus, mutation status and pancreatic cancer were classified by family rather than according to individual relatives.

The distribution of the identified mutations throughout the gene, the types and frequencies of the different types of mutations, and the evidence for patterns of mutations were evaluated. The nonparametric Wilcoxon-Mann-Whitney, Jonckheere-Terpstra, or Kruskal-Wallis tests, as implemented in the computer program StatXact (version 4.01, 1989-1999), were used to test the hypotheses of no differences in the distribution of CDKN2A mutations or families with CDKN2A mutations for the factors of interest. All statistical tests were two-sided.

RESULTS

Table 1 presents the published germline CDKN2A mutations identified in familial melanoma kindreds including the numbers of families with each mutation, their geographical origin and the number reported to have pancreatic cancer. About 70 percent of the mutations have been observed only once, while the remainder has repeatedly been found in different families (figure 1). The most common recurrent mutations are p.G101W, c.225_243del19 (p.P75fs), p.R112_L113insR, p.M53I, p.R24P and p.V126D. The distribution of pancreatic cancer in these families differed significantly (p=0.02); the frequency of pancreatic cancer varied from $\geq$ 30% in p.G101W, p.P75fs, p.R112_L113insR, and p.V126D families to <10% in p.R24P and p.M53I families (figure 1).

Table 1. Familial Melanoma and CDKN2A Mutations: Location and type of mutation, plus numbers of families with each mutation and their geographic origins

Location of Mutation	CDKN2A Nucleotide Change[1]	CDKN2A/p16 Amino acid change[2]	Type of Mutation [p16 protein]	CDKN2A/ p14ARF Nucleotide/ Amino acid change	Type of Mutation [$p14^{ARF}$ protein]	No. families [No. families with pancreatic cancer]	Geographic Origin[3]	References
5'UTR	c. –34G>T		Initiation	N/A	N/A	5 [2]	Au, Ca	Liu et al., 1999; Bishop et al., 2002
Exon								
1α	c.6_29del24		In-frame deletion	N/A	N/A	1	Au	Bishop et al., 2002
1α	c.24_47dup24		In-frame insertion	N/A	N/A	5	Au, GB, US	Flores et al., 1997; Newton-Bishop et al., 1999; Bishop et al., 2002
1α	c.44G>A	p.W15X	Nonsense	N/A	N/A	1	US	Fitzgerald et al., 1996
1α	c.45G>A	p.Wl5X	Nonsense	N/A	N/A	1	Au	Holland et al., 1999
1α	c.46delC	p.L16fs	Frameshift	N/A	N/A	1	Au	Flores et al., 1997
1α	c.47T>G	p.L16R	Missense	N/A	N/A	1	US	Goldstein et al., 2000
1α	c.47T>C	p.L16P	Missense	N/A	N/A	2 [1]	Au, Fr	Soufir et al., 1998; Bishop et al., 2002
1α	c.57_62ins6		In-frame insertion	N/A	N/A	1	Fr	Soufir et al., 1998
1α	c.68G>A	p.G23D	Missense	N/A	N/A	2	Fr, It	Soufir et al., 1998; Fargnoli et al., 1998
1α	c.71G>C	p.R24P	Missense	N/A	N/A	12 [1]	Au, Fr, GB, It, US	Fargnoli et al., 1998; MacKie et al., 1998; Soufir et al., 1998; Holland et al., 1999; Newton-Bishop et al., 1999; Della Torre et al., 2001; Mantelli et al., 2002; Lynch et al., 2002
1α	c.78insG	p.E27fs	Frameshift	N/A	N/A	1 [1]	US	Lynch et al., 2002
1α	c.88delG	p.A30fs	Frameshift	N/A	N/A	1	GB	Newton-Bishop et al., 1999
1α	c.95T>C	p.L32P	Missense	N/A	N/A	2	Au	Flores et al., 1997; Bishop et al., 2002
1α	c.104G>C	p.G35A	Missense	N/A	N/A	2	Au, Fr	Flores et al., 1997; Soufir et al., 1998
1α	c.106G>C	p.A36P	Missense	N/A	N/A	1	Au	Holland et al., 1999
1α	c.132T>A or C>G	p.Y44X	Nonsense	N/A	N/A	1	GB	MacKie et al., 1998
1α	c.142C>A	p.P48T	Missense	N/A	N/A	1	It	Della Torre et al., 2001
1α	c.143C>T	p.P48L	Missense	N/A	N/A	1	Sw	Platz et al., 1997
1α	c.146T>G	p.I49S	Missense	N/A	N/A	2 [1]	Au, Ca	Holland et al., 1999; Lal et al., 2000a, b
1α	c.149A>G	p.Q50R	Missense	N/A	N/A	1	Au	Flores et al., 1997
1α	c.149A>C		Splicing	N/A	N/A	1 [1]	US	Lynch et al., 2002
1β	~14 kb del		N/A	p.Ex1βdel	Deletion	1	GB	Randerson-Moor et al., 2001
1β	c.334G>C	N/A	N/A	p.G112R	Splicing	1	GB	Hewitt et al., 2002
2	c.159G>C	p.M53I	Missense	p.D68H	Missense	16	Au, Ca, Fr, GB, US	Fitzgerald et al., 1996; Flores et al., 1997; MacKie et al., 1998; Monzon et al., 1998;

Location of Mutation	CDKN2A Nucleotide Change[1]	CDKN2A/p16 Amino acid change[2]	Type of Mutation [p16 protein]	CDKN2A/ p14ARF Nucleotide/ Amino acid change	Type of Mutation [$p14^{ARF}$ protein]	No. families [No. families with pancreatic cancer]	Geographic Origin[3]	References
								Soufir et al., 1998; Holland et al., 1999; Newton-Bishop et al., 1999; Goldstein et al., 2000; Tsao et al., 2000
2	c.166_223del58	p.S56fs	Frameshift	1-70p14:76-156p16	Chimera[4]	1	US	Fitzgerald et al., 1996
2	c.167G>T	p.S56I	Missense	p.Q70H	Missense	2	Ca, Fr	Soufir et al., 1998; Monzon et al., 1998
2	c.167_197del31	p.S56fs	Frameshift	1-70p14:67-156p16	Chimera[4]	1	US	Goldstein et al., 2000
2	c.170C>T	p.A57V	Missense	c.213C>T	Silent	1	Fr	Soufir et al., 1998
2	c.172C>T	p.R58X	Nonsense	p.P72L	Missense	1	US	Hussussian et al., 1994; Goldstein et al., 2000
2	c.176T>G	p.V59G	Missense	p.S73R	Missense	2	Fr, Sp	Soufir et al., 1998; Ruiz et al., 1999
2	c.185_208del24		In-frame deletion	c.36_59del24	In-frame deletion	1	Sw	Hashemi et al., 2000
2	c.185T>C	p.L62P	Missense	c.228T>C	Silent	1	Fr	Soufir et al., 1998
2	c.199G>A	p.G67S	Missense	p.R81Q	Missense	1	Au	Holland et al., 1999
2	c.199G>C	p.G67R	Missense	p.R81P	Missense	1	GB	Newton-Bishop et al., 1999
2	c.201delC	p.G67fs	Frameshift	1-82p14:69-156p16	Chimera[4]	1	It	Grammatico et al., 2001
2	c.202_203GC>TT	p.A68L	Missense	p.R82L	Missense	1	Fr	Soufir et al., 1998
2	c.212A>G	p.N71S	Missense	c.255A>G	Silent	4	Au, It, US	Goldstein et al., 2000; Della Torre et al., 2001; Mantelli et al., 2002; Bishop et al., 2002
2	c.212A>T	p.N71I	Missense	p.Q85H	Missense	1	It	Fargnoli et al., 1998
2	c.213C>A	p.N71K	Missense	p.L86M	Missense	1 [1]	Fr	Soufir et al., 1998
2	c.225_243del19	p.P75fs	Frameshift	1-90p14:82-156p16	Chimera[4]	21 [7]	Au, NL, US	Gruis et al., 1995a, 1995b; Holland et al., 1999; Goldstein et al., 2000; Vasen et al., 2000
2	c.240_253del14	1-80p16:100-133p14	Chimera[4]	p.T95fs	Frameshift	4 [1]	US	Ohta et al., 1994; Fitzgerald et al., 1996; Goldstein et al., 2000
2	c.250G>T	p.D84Y	Missense	p.R98L	Missense	1	Sp	Ruiz et al., 1999
2	c.260G>C	p.R87P	Missense	c.303G>C	Silent	4 [2]	US, Sp	Hussussian et al., 1994; Ruiz et al., 1999; Goldstein et al., 2000; Lynch et al., 2002
2	c.285_296del12		In-frame deletion	c.136_147del12	In-frame deletion	1	US	Yarbrough et al., 1996
2	c.290T>G	p.L97R	Missense	c.333T>G	Silent	1 [1]	Fr	Soufir et al., 1998
2	c.296G>C	p.R99P	Missense	c.339G>C	Silent	1 [1]	Fr	Soufir et al., 1998
2	c.301G>T	p.G101W	Missense	p.R115L	Missense	22 [9]	Au, Fr, Is/It, It, Sp, US	Hussussian et al., 1994; Kamb et al., 1994; Whelan et al., 1995; Soufir et al., 1998; Ghiorzo et al., 1999; Holland et al., 1999;

Location of Mutation	CDKN2A Nucleotide Change[1]	CDKN2A/p16 Amino acid change[2]	Type of Mutation [p16 protein]	CDKN2A/ p14ARF Nucleotide/ Amino acid change	Type of Mutation [$p14^{ARF}$ protein]	No. families [No. families with pancreatic cancer]	Geographic Origin[3]	References
								Ruiz et al., 1999; Nagore et al., 2000; Yacobson et al., 2000; Della Torre et al., 2001; Bishop et al., 2002; Mantelli et al., 2002
2	c.310_315del6		In-frame deletion	c.355_360del6	In-frame deletion	1	Ca	Liu et al., 1995
2	c.319C>T	p.R107C	Missense	p.A121V	Missense	1	US	Fitzgerald et al., 1996
2	c.322G>A	p.D108N	Missense	p.R122Q	Missense	1	Au	Flores et al., 1997
2	c.334C>G	p.R112G	Missense	p.P126R	Missense	1	Au	Holland et al., 1999
2	c.337_338 insGTC		In-frame insertion	p.S127_A128 insS	In frame insertion	17 [6]	Sw	Borg et al., 1996; Platz et al., 1997; Borg et al., 2000; Hashemi et al., 2000
2	c.341C>T	p.Pll4L	Missense	c.384C>T	Silent	1	It	Fargnoli et al., 1998
2	c.344T>G	p.V115G	Missense	c.387T>G	Silent	1	Sw	Hashemi et al., 2000
2	c.352G>A	p.A118T	Missense	p.G132D	Missense	1	GB	Newton-Bishop et al., 1999
2	c.358delG	p.E120fs	Frameshift	N/A	N/A	1	Sp	Ruiz et al., 1999
2	c.365G>T	p.G122V	Missense	N/A	N/A	1	Is/Gr	Yacobson et al., 2000
2	c.373G>C	p.D125H	Missense	N/A	N/A	1	Au	Holland et al., 1999
2	c.377T>A	p.V126D	Missense	N/A	N/A	10 [3]	Ca, Fr, It, US	Hussussian et al., 1994; Kamb et al., 1994; Soufir et al., 1998; Goldstein et al., 2000, 2001; Mantelli et al., 2002
2	c.379G>C	p.A127P	Missense	N/A	N/A	1 [1]	US	Lynch et al., 2002
2	c.457G>T		Splicing	p.1-65p14:154-156p16	Splicing	2 [2]	US	Lynch et al., 2002; Rutter et al., 2003
1α,1β,2,3	All deleted		Whole gene deletion	p.Ex1βdel	Deletion	1	Fr	Bahuau et al., 1998
1α,1β,2,3	All deleted		Whole gene deletion	p.Ex1βdel	Deletion	1	US	Bahuau et al., 1998
Intron								
1	c.IVS1-1G>C		Splicing			1	It	Petronzelli et al., 2001
2	c.IVS2-105A>G		Splicing	N/A	N/A	6	GB	Harland et al., 2001
2	c.IVS2+1G>T	p.R128fs**;** p.Ex1a-Ex3delEx2	Splicing	p.1-65p14:154-156p16	Splicing	1 [1]	US	Hussussian et al., 1994; Rutter et al., 2003

[1]GenBank: NM_000077.2. Mutations numbered with the A of the initiation codon as +1 unless otherwise noted. See also www.wmi.usyd.edu.au:8080/melanoma.html

[2]Changes listed for missense, frameshift, and nonsense mutations.

[3]Country: Au=Australia, Ca=Canada, Fr=France, GB=Great Britain, Gr=Greece, Is=Israel, It=Italy, NL=Netherlands, Sp=Spain, Sw=Sweden, US=United States.

[4]Mutations involving chimeric proteins follow the approach proposed by Fung et al., 2002.

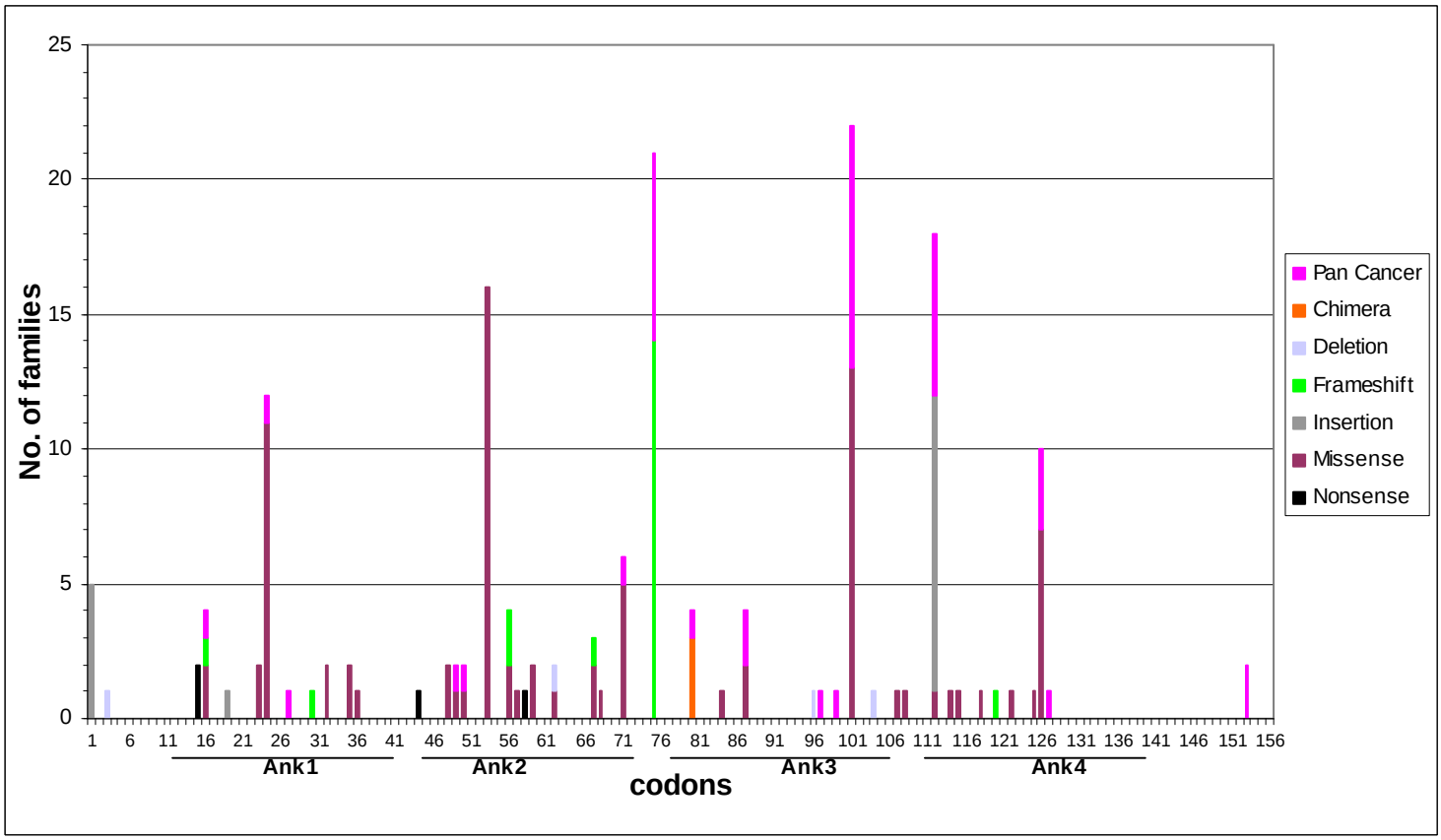

Figure 1. Number of melanoma-prone families with CDKN2A mutations in the coding region of p16, listed by codon (1-156). Codon numbering for the mutations is taken from table 1. Insertions, deletions, and frameshift mutations are shown at the codon in which the mutation. starts. The chimera mutation (Fung et al., 2002) is a deletion that produces a fusion protein that includes both p16 and $p14^{ARF}$; it is presented at the last codon in the p16 portion of the protein. Families with reported pancreatic cancer are represented in pink for all mutation types.

Table 2 shows the location (Table 2A) and types (Table 2B) of the mutations in families with and without reported pancreatic cancer. For both groups of families, almost 90% of the mutations occurred in the coding region of exons 1α and 2. The majority of mutations were missense mutations (56%). For families without reported pancreatic cancer, frameshift mutations (12%) and deletions (12%) were the next most common types of mutations. For families with pancreatic cancer, splicing (17%) and frameshift (11%) mutations followed missense mutations in frequency.

To further examine the families with and without reported pancreatic cancer, the types and locations of CDKN2A mutations (or families) were compared. The results showed no significant differences in the types (p=0.63) of mutations, mutation location across exons (p=0.77), or the four ankyrin repeats (p=0.33). Whether or not the mutation produced an amino acid change in p14ARF also showed no significant difference in mutations (p=0.60) or families (p=0.38). However, there was a significant difference (p=0.002) in the numbers of families with mutations across the four ankyrin repeats. There were fewer families with pancreatic cancer in Ank1 and Ank2 compared to Ank3 and Ank4. Restricting this analysis to the 23 families in which the pancreatic cancer patient was shown to have a CDKN2A mutation yielded similar results (p=0.01). Finally, since some mutations (e.g. frameshift) might affect more than one Ank repeat, families with these mutations were included in each Ank repeat that was altered. Excluding these families (n=29) from the analysis had no effect on the results (p=0.002).

Table 2. Location and Types of CDKN2A Mutations in Familial Melanoma Kindreds by Presence or Absence of Pancreatic Cancer

A. Location of mutations

Location	*No reported Pancreatic Cancer*		*Reported Pancreatic Cancer*	
	# Mutations (%)	# Families (%)	# Mutations (%)	# Families (%)
Exon 1a	19 (32)	36 (24)	5 (28)	5 (12)
Exon 1ß	2 (3)	2 (1)	--	--
Exon 2	33 (56)	97 (66)	11 (61)	34 (81)
Initiation	1 (2)	3 (2)	1 (6)	2 (5)
Intronic	2 (3)	7 (5)	1 (6)	1 (2)
Whole gene del	2 (3)	2 (1)	--	--
Total	59 (99*)	147 (99*)	18 (101*)	42 (100)

Numbers of mutations and numbers of families with each mutation (with percentages in parentheses) are presented.

* Percentage (%) does not total 100 because of rounding error.

B. Types of Mutations

Type	*No reported Pancreatic Cancer*		*Reported Pancreatic Cancer*	
	# Mutations (%)	# Families (%)	# Mutations (%)	# Families (%)
Missense	33 (56)	85 (58)	10 (56)	21 (50)
Frameshift	7 (12)	20 (14)	2 (11)	8 (19)
Splicing	3 (5)	8 (5)	3 (17)	4 (10)
Nonsense	4 (7)	4 (3)	--	--
Deletion:			--	--
In-frame	4 (7)	4 (3)		
Whole gene	2 (3)	2 (1)		
Exon 1ß	1 (2)	1 (1)		
Insertion (in-frame)	3 (5)	17 (12)	1 (5.5)	6 (14)
Initiation	1 (2)	3 (2)	1 (5.5)	2 (5)
Chimera	1 (2)	3 (2)	1 (5.5)	1 (2)
Total	59 (101*)	147 (101*)	18 (100.5*)	42 (100)

Numbers of mutations and numbers of families with each mutation (with percentages in parentheses) are presented.

* Percentage (%) does not total 100 because of rounding error.

DISCUSSION

Sixty-seven different germline CDKN2A mutations identified in 189 melanoma-prone families were evaluated. The majority of mutations observed were missense (56%) mutations. About 70% of the mutations were observed only once, while the remainder has repeatedly been found in different families. Haplotype analyses of the common recurrent mutations (e.g. c.-34G>T, p.R24P, p.M53I, p.P75fs, p.G101W, p.R112_L113insR, p.V126D) have shown that the majority result from single genetic origins, i.e. common founders or ancestors (Gruis et al., 1995a, 1995b; Borg et al., 1996; Platz et al., 1997; Pollock et al., 1998; Liu et al., 1999; Ciotti et al., 2000; Goldstein et al., 2000, 2001; Auroy et al., 2001; Hashemi et al., 2001;) rather than mutation hotspots in the CDKN2A gene. To date, only one recurrent mutation has been shown to have multiple origins (c.24_47dup24) (Pollock et al., 1998). The insertion, a 24 base pair (bp) duplication, was hypothesized to have arisen as a result of unequal crossing over between the two 24-bp repeats that occur naturally in the wild-type sequence. This mutation would be more likely to recur because of the inherent instability of the tandem repeat region that produced the 24 base pair insertion (Pollock et al., 1998).

Several studies have demonstrated an increased risk of pancreatic cancer among melanoma-prone families with CDKN2A mutations (Bergman et al., 1990; Goldstein et al., 1995; Bergman and Gruis, 1996; Ghiorzo et al., 1999;

Borg et al., 2000; Vasen et al., 2000) but the precise relationship between the CDKN2A gene and pancreatic cancer remains unknown. At present, it is not possible to predict what genotype or phenotype predisposes an individual to pancreatic cancer in these families. Although the distribution of mutation types suggested possible differences between the two groups of families with splicing mutations appearing more frequent in families with pancreatic cancer (17%) compared to those without reported pancreatic cancer (5%), the results were not statistically significant. Interestingly, among pancreatic cancer patients and/or families without familial CMM but with CDKN2A mutations, two out of the 7 reported CDKN2A mutations were splicing mutations (Moskaluk et al., 1998; Gerdes et al., 2000; Moore et al., 2000; Lal et al., 2000a; Barsch et al., 2002; Lynch et al., 2002).

The distribution of pancreatic cancer in CDKN2A melanoma-prone families with common founder mutations differed significantly. In addition, there was a significant difference in the numbers of families without reported pancreatic cancer compared to the melanoma-prone families with pancreatic cancer across the four ankyrin repeats. Removal of the common founders (i.e. p.R24P, p.M53I, p.P75fs, p.G101W, p.R112_L113insR, p.V126D) from this analysis eliminated the significant findings for the Ank repeats (p=0.50), as expected, since about half of the families without pancreatic cancer and 62% of the families with pancreatic cancer had these six common founder mutations. Additional studies are needed to further evaluate these findings.

This study had two major limitations. First, since the study was restricted to data published through 2002, incomplete reporting of CDKN2A mutations in melanoma-prone families and/or pancreatic cancer occurrence (i.e., publication or reporting bias) could potentially bias the results. Second, individual data was unavailable for many publications and so the unit for analysis was the family. It was, thus, not possible to evaluate the numbers of melanoma patients with specific mutations or the distributions of pancreatic cancer patients in melanoma-prone families with CDKN2A mutations. In addition, even though pancreatic cancer was reported in 42 familial melanoma kindreds, determination of mutation status was accomplished for only 55% of the families. However, the subset of families (n=23) for which mutation status was known for the pancreatic cancer patients showed similar results to the 42 total reported kindreds with pancreatic cancer.

In summary, comparison of CDKN2A melanoma-prone families with and without reported pancreatic cancer, using published data, suggested possible differences between the two groups of families. Whether the observed patterns represent etiologic differences or reflect incomplete reporting of pancreatic cancers in melanoma-prone families with CDKN2A mutations or incomplete publication of melanoma-prone families with CDKN2A mutations awaits further studies that are able to use genotypic and phenotypic information on individual family members. And as has been shown previously for breast cancer, ovarian cancer, and BRCA1/2 mutations (Gayther et al., 1995; 1997; Thompson and Easton, 2001; Thompson et al., 2002) large numbers of individuals and families will be required to accomplish these tasks.

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